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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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EXAMINER	
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ART UNIT	PAPER NUMBER
1635	

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Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/721,693	KAEMMERER, WILLIAM F.	
	Examiner	Art Unit	
	Louis V. Wollenberger	1635	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *05 January 2006*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1,5,9,10,14,19,24,25 and 85-89* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1, 5, 9, 10, 14, 19, 24, 25, and 85–89* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Response to Non-Final Office Action

Applicant's response filed January 5, 2006, has been considered. The following Final Office Action is offered in reply. Rejections and/or objections not reiterated from the previous Office Action mailed on October 4, 2005, are hereby withdrawn. The following rejections and/or objections are either newly applied or are reiterated and are the only rejections and/or objections presently applied to the instant application.

The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office Action.

Amendments

Applicant's amendments to the claims, amending Claim 1, withdrawing claims 11–13, 15, and 23, and adding new claims 85–89 are acknowledged. Also acknowledged are Applicant's amendments to page 1 of the specification, inserting a cross-reference to related applications to which benefit is claimed. The amendments are entered into the application.

Status of the Application

Claims 1, 5, 9, 10, 14, 19, 24, 25, and new claims 85–89 are pending and currently under examination. New claims 85–89 are considered by the Examiner to be supported by the instant application and to belong to the elected Group.

Priority

Applicant's claim for domestic priority under 35 U.S.C. 119(e) is acknowledged. However, U.S. Provisional application 60/429,387, upon which benefit is claimed fails to provide adequate support under 35 U.S.C. 112 for claims drawn to medical systems comprising small interfering RNA, Claims 1, 5, 9, 10, 14, 19, 24, 25, and 85–89. The instant application clearly defines small interfering RNA (pages 14-15) as "double stranded RNA agents" that are "used to trigger RNA interference." As ordinarily used in the art, "small interfering RNA" normally refers to double stranded RNAs, which operate by a different biochemical pathway than ribozymes and antisense (single stranded) RNAs. Thus, antisense, ribozymes, and small interfering RNA are considered to represent distinct molecular agents. The earliest filed priority document in which adequate support is provided for medical systems comprising small interfering RNA is U.S. Provisional application 60/444, 614, filed 2/3/03. If applicant believes that support for the instant claims, drawn to medical systems comprising small interfering RNA agents, is present in the earlier filed priority document, applicant must, in responding to this Action, point out with particularity, where such support may be found.

Claim Objections (withdrawn)

Objections to Claims 1, 5, 9–15, 19, and 23–25 because the claims appear to be drawn to a medical device or apparatus, yet the preamble recites a medical "system," which may refer to an apparatus or a method, are withdrawn for the following reasons:

The instant claims do not recite a method comprising steps but instead recite a manufacture comprising a group of interrelated elements, which, in combination, may be used

for treating a neurodegenerative disorder. Accordingly, the Examiner agrees with Applicants that no confusion exists as to the statutory class of invention.

Claim Objections (new)

New claims 85, 86, 88, and 89 are objected to because of grammatical informalities. For convenience, the claims are reproduced below.

> 85. (new) A medical system of claim 1 wherein said small interfering RNA which is able to inhibit expression of ataxin-l.
> 86. (new) A medical system of claim 1 wherein said small interfering RNA is inhibits the activity of ataxin-l.
>
> 88. (new) A medical system of claim 1 wherein said small interfering RNA is of sufficient length and that comprises any one of SEQ ID Nos: 1-6, 13 or 16.
> 89. (new) A medical system of claim 1 wherein said small interfering RNA that is able to stably interact with the ataxin-l mRNA.

Claim 85, when read together with "WE CLAIM," is not considered to represent a complete sentence.

Claim 86 recites "is inhibits," which is grammatically awkward and unclear.

Claim 88 recites "and that." It is suggested that the "that" be removed. Claim 88 is further objected to as being drawn to non-elected inventions: SEQ ID Nos:3-6, 13, and 16. (Applicants elected SEQ ID NO:1 and 2 in their response, filed 8/19/05.) Applicants are requested to amend the claim to remove recitations to non-elected inventions.

Claim 89, when read together with "WE CLAIM," is not considered to represent a complete sentence.

Appropriate correction is required.

Claim Rejections - 35 USC § 112 (new)

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

New Claims 87–89 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 87 recites "inhibits levels of ataxin-1 mRNA." It is unclear what is meant by "inhibits levels." How can an siRNA inhibit a level or levels? An siRNA may inhibit expression of a gene and, thereby, *reduce* the level of mRNA. An siRNA may alter the level of mRNA. But it is unclear how an siRNA may inhibit levels. Appropriate correction is required.

Claim 88 recites "of sufficient length." The term "of sufficient length" is a relative term which renders the claim indefinite. The term "of sufficient length" is not defined by the claim, the specification does not provide a standard for ascertaining the requisite degree, and one of ordinary skill in the art would not be reasonably apprised of the scope of the invention.

Claim 89 recites a "small interfering RNA that is able to stably interact with the ataxin-1 mRNA. It is unclear what is meant by "stably interact." The term " stably interact" is not defined by the claim, the specification does not provide a standard for ascertaining the requisite degree, and one of ordinary skill in the art would not be reasonably apprised of the scope of the invention.

Additionally, Claim 89 recites the limitation "the ataxin-1" in line 2. There is insufficient antecedent basis for this limitation in the claim.

Appropriate correction is required.

Double Patenting

Claims 1, 9–15, 19, and 25 remain rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 7, 8, 16, 17, and 29 of copending Application No. 10/962,732 (US 2005/0048641) in view of Paxinos et al. (2001) *The Mouse Brain in Stereotaxic Coordinates.* Academic Press, 2nd Ed; and Cahill et al. (1995) *Atlas of Human Cross-sectional Anatomy*, Wiley-Liss, 3rd ed.

Although the conflicting claims are not identical, they are not patentably distinct from each other for the following reasons.

Copending application No. 10/962,732 and the instant application are both directed to a medical device, or system, for transfusing interfering RNA (siRNA) into tissues and cells in living organisms, including humans. Claim 1 of the instant application recites a medical system for treating a neurodegenerative disorder "in a patient," comprising an intracranial access device, a mapping means, a deliverable amount of siRNA or vector encoding siRNA, and a delivery means. Claims 9 and 10 limit claim 1 by stating that the access device is a catheter or access port. Claim 19 limits claim 1 by stating that the siRNA targets SCA1 mRNA. Claim 25 limits claim 1 by stating that the delivery means is an infusion pump.

Claims 7, 8, 16, 17, and 29 of copending Application No. 10/962,732 recite a similar system for delivering small interfering RNA targeted to a gene, SCA1, associated with a neurodegenerative disease. Claim 7, the base claim, recites a system comprising an implantable infusion pump, a reservoir, a fluid comprising an RNAi agent, and a catheter. The implantable infusion pump is defined as being either implantable or external, may have a port into which a needle can be inserted to inject a therapeutic agent, and may further have a catheter, and a

catheter port (paragraph 24) for delivering an RNAi agent to a specific location in the brain. Paragraph 29 describes a specific embodiment of the claimed system; namely, intraparenchymal and intracerebroventricular delivery devices (illustrated in Fig. 3) for delivering agents to the brain, and clearly embodies an access port and catheter. Thus, the device claimed by claims 7, 8, 16, 17, and 29 of copending Application No. 10/962,732 may serve to deliver siRNA intracranially to different regions of the brain and is, therefore, considered to encompass "medical systems" such as those claimed in the instant application.

Furthermore, Applicant states on page 28 of the instant application (10/721,693) that "The envisioned route of delivery is through the use of implanted, indwelling, intraparenchymal catheters that provide a means for injecting small volumes of fluid containing AAV or other vectors directly into local brain tissue." On page 29 of the instant application, Applicant states that "...the present invention includes the delivery of small interfering RNA vectors using an implantable pump and catheter, like that taught in U.S. Patent No. 5,735,814 and 6,042,579..."

Copending Application No. 10/962,732 does not claim a "mapping means" or means for locating a predetermined location in the brain. However, it would be obvious to one of skill in the art to combine the teachings of copending Application No. 10/962,732 with those of a standard anatomical atlas such as that of Cahill et al. or Paxinos et al., who provide not only an anatomical guide of the mouse brain but also stereotaxic coordinates for different brain locations. These anatomical atlases may serve as a means for mapping predetermined locations in the brain. A review of the List of Structures in the Paxinos et al. reference shows that several of the "predetermined locations" recited in claims 11-13 and 15 are described. These include, the substantia nigra, the cerebral cortex, the hippocampus, the striatum (caudate putamen), the

subthalamic nucleus, and the medial (fastigial) cerebellar nucleus. The Atlas of Human Anatomy, by Cahill et al., shows some of alternative recited structures; specifically, Cahill et al. teach the location of the dentate nucleus, enabling the skilled artisan to position the implantable infusion pump and catheter in a manner that would deliver the siRNA to the desired brain location.

Accordingly, one of skill in the art would conclude that the invention defined in the instantly claimed invention of this application (No. 10/852,997) is an obvious variation of the invention defined in copending Application No. 10/721,693 since each of the required elements are present and each of the devices or systems is clearly intended to serve as a system for delivering small interfering RNA (specifically siRNA targeting SCA1 mRNA) intracranially to treat a neurodegenerative disease.

Thus in the absence of evidence to the contrary, the instantly claimed invention as a whole would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made.

This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

Arguments considered:

Applicants argue that it is improper to cite additional references in a provisional obviousness-type double patenting rejection and that Paxinos and Cahill fail to teach Applicants' mapping means.

In particular, Applicants argue that an anatomical map, such as that provided by Paxinos et al., is a useful teaching tool in gross anatomy, but is inadequate for mapping live brains.

> "Placing a delivery device into the live brain of a patient requires exquisite preciseness that can not be obtained from just looking at the maps and coordinates of Paxinos and Cahill. Applicants mapping means is related to precise live coordinates and structures in a patient that are generated for each individual brain. As you may know, there is an infinite variation of head sizes, shapes, and brain anatomy. Applicant's mapping means is tied to live mapping systems of a patient's brain." (Applicants' Remarks, pp. 6-7)

With regard to the propriety of the rejection, Applicants are referred to MPEP §804, Section II.B.1, which states

> "A double patenting rejection of the obviousness-type is "analogous to [a failure to meet] the nonobviousness requirement of **35 U.S.C. 103**" except that the patent principally underlying the double patenting rejection is not considered prior art. *In re Braithwaite*, 379 F.2d 594, 154 USPQ 29 (CCPA 1967). Therefore, any analysis employed in an obviousness-type double patenting rejection parallels the guidelines for analysis of a **35 U.S.C. 103** obviousness determination. *In re Braat*, 937 F.2d 589, 19 USPQ2d 1289 (Fed. Cir. 1991); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985)."

Applicants are also referred to Form Paragraph 8.37 and the Examiner notes that go with it, which provide for circumstances in which a secondary reference is used to complete the provisional obviousness-type rejection. The rejection is, therefore, considered to be proper.

With regard to Applicants' assertion that the Paxinos et al. and Cahill et al. references are insufficient for use in the claimed invention as a whole, the Examiner reminds Applicants that broadest reasonable interpretation of "mapping means for locating a predetermined location in the brain of a patient," according 35 USC §112, sixth paragraph, includes the corresponding structure described in the specification and equivalents thereof." (See MPEP §2181, Section II, for example)

> II. WRITTEN DESCRIPTION NECESSARY TO SUPPORT A CLAIM LIMITATION WHICH INVOKES 35 U.S.C. 112, SIXTH PARAGRAPH
> 35 U.S.C. **112**, sixth paragraph states that a claim limitation expressed in means-plus-function language "shall be construed to cover the corresponding structure.described in the specification and equivalents thereof." "If one employs means plus function language in a claim, one must set forth in the specification an adequate disclosure showing what is meant by that language. If an applicant fails to set forth an adequate disclosure, the applicant has in effect failed to particularly point out and distinctly claim the invention as required by the second paragraph of section **112**." *In re Donaldson Co.*, 16 F.3d 1189, 1195, 29 USPQ2d 1845, 1850 (Fed. Cir. 1994) (in banc).

A review of the instant application fails to find any disclosure clearly describing the corresponding structures, apparatus, or devices intended by Applicants to be used as a "means for mapping a predetermined location in the brain of a patient" in the claimed invention. Thus, no guidance is given as to what does or does not constitute a "means for mapping." Therefore, the Examiner must interpret the recitation to include any technically feasible, practical means for locating a predetermined location in the brain of a patient. While Applicants have amended the claims to recite "in a patient" and "of a patient," this limitation does not distinguish the invention over the applied references. The specification, in fact, defines "patient" as "an organism, which is a donor or recipient of explanted cells or the cells themselves." (Specification, page 12).

> "Patient" also refers to an organism to which the nucleic acid molecules of the invention can be administered. Preferably, a patient is a mammal or mammalian cells, e.g., such as humans, cows, sheep, apes, monkeys, swine, dogs, cats, and the like, or cells of these animals used for transplantation. More preferably, a patient is a human or human cells." (Specification, page 12)

Thus, according to the Specification, a "patient" is any organism, including a mouse or a rat. Paxinos et al. is a reference specifically designed for mouse brain research that requires the worker to locate, treat, and/or manipulate specific locations in the mouse brain. It is quite clear that Paxinos et al. is designed to be used in conjunction with stereotactic frames, mounted on the heads of the animals, and that one of skill in the art would know that the coordinates given in Paxinos et al. are for adult or age-specific animals, and that allowances and/or adjustments in the coordinates may be necessary depending on the age of the animal being used. Furthermore, the instant claim does not specify or require any minimum degree of precision that must be obtained with the recited "mapping means." It is sufficient that the mapping means would enable the researcher to target any structure or general region in the brain: the forebrain or hindbrain, for example.

Paxinos et al is clearly designed for assisting researchers with surgical procedures on live animals to enable the researcher to deliver or implant materials in specific locations in the brain of a mouse, or a rat, depending on the atlas. Paxinos et al. give precise stereotaxic coordinates, which enable delivery to specific locations in the brain when used in conjunction with a stereotactic frame.

Nothing in the claims or the specification excludes the use of an anatomical atlas or stereotactic frame and it is clear that stereotaxic coordinates, such as those provided by Paxinos et al., are routinely used by researchers to implant devices and delivery reagents into the brains of mice and rats for investigational purposes.

For instance, the instant application (page 28), under "Devices," states "Delivery occurs through a stereotactically implanted polyurethane catheter." Whitesell et al. state that rats with stereotactically implanted catheters were used for their experiments (page 4666). Dorri et al. state that "A guide cannula was inserted into the left hippocampus using coordinates given in Paxinos and Watson ... adjusted for the young age of the animals (1.8 mm lateral, 4.16 mm posterior, 2.7 mm ventral). (page 49) Zhang et al. (1996) state that "Mice were anesthetized with halothane and the phosphorothioate dopamine receptor antisense oligonucleotide labeled with FITC ...was injected stereotactically into the lateral cerebral ventricle using a plastic mold ..." (page 14) Thus, it is clear that many researchers in the field of brain research have relied on Paxinos et al. or similar stereotaxic atlases as references to deliver materials to specific locations in the brains of mice and rats.

If, as Applicants assert, anatomical atlases, which give precise 3-D stereotaxic coordinates of brain structures, are not within the scope of the recitation "means for mapping,"

and such atlases are unsuitable for use in the claimed invention, what is within the scope of the recitation? What does a "means for mapping" consist of? What is it? What does it look like? Would one of skill in the art know what does or does not fall within the scope of the recitation "means for mapping"? The specification gives neither general guidance nor specific examples of any structure clearly informing one of skill in the art what does or does not constitute "a mapping means for locating a predetermined location in the brain of a patient."

Accordingly, the instant rejection is maintained.

Claim Rejections - 35 USC § 103

Claim 1 remains rejected under 35 U.S.C. 103(a) as being unpatentable over Xia et al. (2002) *Nature* 20:1006–1010 (cited in IDS); Driscoll et al. (WO 01/49844); Paxinos et al. (2001) *The Mouse Brain in Stereotaxic Coordinates.* Academic Press, 2nd Ed; and Cahill et al. (1995) *Atlas of Human Cross-sectional Anatomy*, Wiley-Liss, 3rd ed.

Xia et al. teach a method for intracranial delivery of a vector encoding a small interfering RNA (siRNA). Specifically, Xia et al. teach a method for silencing gene expression *in vivo* in the brain of a mouse using a recombinant adenovirus encoding small interfering RNA (page 1007). In a pilot experiment (described on pp. 1007-8), Xia et al. used a virus encoding siRNA specific for green fluorescent protein (GFP) to silence eGFP expression in transgenic mice that express eGFP endogenously in their brain tissue. Xia et al. state that the recombinant virus was "injected" into the brain, specifically the brain striatal region (page 1007, 1010). Thus, Xia et al. delivered the vector directly to the brain by "injection." This is taken to mean that a delivery means, such as a syringe, was used to inject the siRNA-encoding vector into the brains of the

mice subjects. The device is therefore considered to have functioned both as "an intracranial access device" and as "a delivery means," as recited in the instant claim. Xia et al. state that the virus also contained a dsRed expression cassette, which allowed for unequivocal localization of the injection site by fluorescence microscopy. Thus, "a mapping means" or means for mapping a "predetermined location in the brain" is also present in the Xia et al. system.

Xia et al. show that GFP expression was reduced in the injected hemisphere only (page 1007). Thus, Xia et al. teach a "system" for reducing gene expression in the brain using a vector encoding a small interfering RNA, specifically, a 21-bp hairpin RNA—i.e., a double stranded, interfering RNA—targeting eGFP (page 1009); and also encoding dsRed, to serve as a "mapping means."

Xia et al. further state that their results support the idea that "hairpin RNA can reduce target gene expression through siRNA-mediated mechanisms." (page 1009, 1st column) and go on to suggest that "One powerful therapeutic application of siRNA would be to reduce expression of toxic gene products in dominantly inherited diseases such as polyglutamine (polyQ) neurodegenerative disorders." (page 1008, 2nd column) This suggests that one of skill could use siRNA encoding vectors *in vivo* to reduce endogenous gene expression in the brain, as shown by Xia et al. See also page 1009, 2nd column. Thus, Xia et al. clearly teach a system within the scope of Claim 1 that is suitable for treating a neurodegenerative disease using small interfering RNA.

Given the teachings of Xia et al., it is likely that one of skill in the art would be mindful of the teachings of Driscoll et al. (cited in Applicant's IDS), who teach methods for making and using vectors encoding short hairpin RNAs targeting genes associated with neurodegenerative

disorders such as Alzheimer's disease, Huntington's disease, and Parkinson's disease (pages 3-5; 41-46). Exemplary vectors are illustrated in Figs. 5 and 6. One vector in particular, expresses an inverted repeat sequence specific for alpha synuclein, a gene associated with Parkinson's gene. Figs. 1 and 2 outline the procedure and principles for preparing and using said shRNA expressing vectors to inhibit gene expression. The expressed RNAs are predicted to form hairpin RNAs, having double stranded structures that mediate gene-specific inhibition via an RNAi mechanism. The vectors are said to be useful in the treatment of diseases such as Alzheimer's to reduce plaque formation.

Xia et al. and Driscoll et al. do not teach how to specifically target predetermined locations in the brain. However, one of skill in the art following the Xia et al. teachings would be expected to refer to an anatomical atlas such as that provided by Paxinos et al., who provide not only an anatomical guide of the mouse brain but also stereotaxic coordinates for different brain locations, which may serve as "mapping means," enabling the skilled artisan to locate predetermined locations in the brain. A review of the List of Structures in the Paxinos et al. reference shows that several of the "predetermined locations" recited in claims 11-13 and 15 are described. These include, the substantia nigra, the cerebral cortex, the hippocampus, the striatum (caudate putamen), the subthalamic nucleus, and the medial (fastigial) cerebellar cortex. The Atlas of Human Anatomy, by Cahill et al., shows some of the alternative recited structures; specifically, Cahill et al. teach the location of the dentate nucleus. The Cahill et al. and Paxinos et al. atlases are considered to be representative of any number of atlases that the skilled artisan might consult to "predetermine" specific locations in the brain.

It would have been obvious to one of ordinary skill in the art at the time the invention was made to combine the teachings of Xia et al., Driscoll et al., Paxinos et al., and Cahill et al. for the reasons given above. Specifically, it would have been obvious to one of skill in the art to inhibit a specific gene target associated with a particular neurodegenerative disorder using an siRNA-encoding vector, as taught by Xia et al. and Driscoll et al. By using the stereotaxic coordinates provided by Paxinos et al. and detailed illustrations shown by Cahill et al., it would have been obvious to the skilled artisan, that said vectors could be used in a direct delivery system such as that taught by Xia et al. to transmit small interfering RNA (e.g., shRNA) to particular brain cells in specific regions of the brain afflicted by the neurodegenerative disease.

One would have been motivated to create and use such vectors because Xia et al. expressly teach that such vectors work to reduce endogenous gene expression and because RNA interference is taught by Xia et al. and Driscoll et al. as having the potential to relieve symptoms associated with neurodegenerative disorders.

Finally, one would have a reasonable expectation of success given that Driscoll et al. expressly describe methods, and give actual examples, for constructing and using shRNA (small hairpin RNA) expressing vectors for purposes of inhibiting the expression of genes associated with neurodegenerative diseases. Further, one of skill in the art armed with such vectors would have a reasonable expectation of success in predetermining a specific location in the brain, given that Paxinos et al. provide specific stereotaxic coordinates and Xia et al. provide a specific working example of how siRNA may be delivered and thereafter localized, or mapped, in the brain.

Thus in the absence of evidence to the contrary, the invention as a whole would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made.

Arguments considered:

Applicants argue (pp. 9-13) that the instant references fail to teach several limitations. However, many of the limitations argued by Applicants are not recited in the instant claim. For instance, Applicants state that Xia et al. does not provide "an active mapping means to determine delivery of live patients and hence could not be used to treat a neurodegenerative disorder" (Remarks, page 9). Applicants state that Driscoll et al. do not teach "where one should target the siRNAs" (Remarks, page 10). Applicants state that Driscoll et al. fail to teach how to treat Alzheimer's Disease using siRNA (Remarks, page 11). Applicants state that Paxinos et al. fail to disclose a mapping means for living patients (Remarks, page 13) and that Xia's use of a dsRed Expression Cassette in cadaver tissue fails to be an equivalent mapping means (Remarks, page 13). The instant claims do not recite these limitations. Moreover, as explained above, Paxinos et al. and Cahill et al. are relied on, in addition to Xia et al., as the "means for locating a predetermined location in the brain." Applicants state that Driscoll et al. and Xia et al. fail to teach siRNAs of suitable size for treatment of disorders (Remarks, page 10). However, the claim does not require siRNAs of any specific size. Small interfering RNAs may be of varying lengths, according to the instant application (page 14). Moreover, Driscoll et al. teach that interfering RNAs may be of 20 to 2500 nucleotides in length (page 11).

Applicants appear to be arguing Claim 1 as though it were drawn to a method. However, as explained above, the Claim is interpreted as being drawn to an interrelated group of elements. Claim 1 does not require a sequential series of steps. For example, Claim 1 does not require the

step of determining the location of a predetermined location in the brain of a patient. The claim does not require that "locating" take place while the patient is still alive. Claim 1 only requires a means for locating a predetermined location in the brain of a patient. Xia et al.'s dsRed vector is considered to be such a mean because it allows one to locate regions in the brain, whether the locating is done before or after delivery of the siRNA, or before or after the patient is deceased. In addition, Paxinos et al. is considered to be a suitable means for locating regions in the brain of a live patient, a mouse, as explained above.

Applicants argue against the references individually; however, one cannot show nonobviousness by attacking references individually where the rejections are based on combinations of references. See *In re Keller*, 642 F.2d 413, 208 USPQ 871 (CCPA 1981); *In re Merck & Co.*, 800 F.2d 1091, 231 USPQ 375 (Fed. Cir. 1986). The question is not whether Xia et al., Driscoll et al., or Paxinos et al. would each have been unsuitable for the task of treating neurodegenerative disorders using siRNA, but what the references as a whole, when taken together, would have taught or fairly suggested to one of skill in the art at the time the invention was made. One motivation to combine the references is the desire of one of skill in the art to understand the relationship between gene expression and neurodegenerative disease, as suggested by Xia et al. and Driscoll et al. Animal models (i.e, mice) are often used in such research, as evidenced by Xia et al., and would have been considered suitable subjects for studies involving siRNA-mediated knockdown of any number of specific gene targets using naked siRNA or vector-encoded siRNA, as taught by Driscoll et al.

The instant references are relied upon for what they taught and for what they reasonably suggested to one of skill in the art at the time the instant invention was made. The instant

invention is drawn to a group of interrelated elements that might be used for any number of different purposes. The instant references disclose all of the limitations in the instant claims and provide ample motivation to combine the limitations to inhibit gene expression in the brains of organisms such as mice, rats, and even *C elegans.* Applicants are reminded that the motivation to combine the teachings of the applied references may be for a purpose different from that recited in the preamble of the instantly claimed invention. It is not necessary that the combined references achieve the same advantage or result discovered by applicant (see MPEP §2144). One of skill in the art reading the instant references may reasonably conclude that small interfering RNAs could be used to study gene function in the brains of animals, whether for understanding neurodegenerative disorders or any other disorder of the brain. Furthermore, only a reasonable expectation of success is required; absolute predictability is not required (MPEP §2132.02). Driscoll et al. is considered to be a general guide for designing and generating hairpin RNA-expressing vectors. It is clear that Driscoll et al. reasonably suggest that hairpin vectors may be used in any number of different organisms for research and/or therapeutic purposes in model animals, for example, to treat any number of disease, including neurodegenerative diseases.

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Claims 1, 5, 9, 10, 19, 24, and 25 remain rejected, and new claims 85–87 and 89 are rejected under 35 U.S.C. 103(a) as being unpatentable over Xia et al. (2002) *Nature* 20:1006–1010; Driscoll et al. (WO 01/49844); Paxinos et al. (2001) *The Mouse Brain in Stereotaxic Coordinates.* Academic Press, 2nd Ed; and Cahill et al. (1995) *Atlas of Human Cross-sectional Anatomy*, Wiley-Liss, 3rd ed., as applied to claims 1 and 11–15 above, and further in view of

Whitesell et al. (1993) *Proc. Natl. Acad. Sci.* 90:4665-4669; Davidson et al. (US Patent Application Publication 2004/0023390); and Matilla et al. (1998) *J. Neuroscience* 18:5508-5516.

Claims 1, 9, 10, 19, and 25 are described above. Claim 5 limits claim 1 by stating that the neurodegenerative disorder is spinocerebellar ataxia type 1. Claim 24 limits claim 1 by stating that the delivery means is injection from an external syringe into an intracranial access port. New claims 85–87 and 89 are drawn to the medical system of claim 1 comprising siRNA that inhibits the expression of ataxin-1.

Xia et al., Driscoll et al., Paxinos et al., and Cahill et al. are relied on for the reasons given above. These references do not specifically teach the use of a catheter or an access port; an siRNA complementary to an mRNA transcript from the SCA1 gene; injection from a syringe into an intracranial access port; or the use of an infusion pump.

Whitesell et al. teach a system for intraventricular administration of radioactively or fluorescently labeled antisense oligonucleotides into rats. (pages 4665-6). The rat subjects are described as containing 22-guage steel cannulae stereotactically implanted in the lateral ventricle (page 4666). The cannulae serve as ports, and for purposes of this examination, are considered to also represent catheters, through which labeled antisense oligos were injected by bolus injection with a Hamilton syringe or continuous injection using a miniosmotic pump (page 4666). ("Catheter" is defined by Merriam-Webster OnLine as a tubular medical device for insertion into body cavities to permit injection of fluids.) Whitesell et al. report that their study supports the feasibility of continuously perfusing the CNS with therapeutic concentrations of intact antisense oligos, and the possibility of using such therapeutics to target leptomeninigeal and intraparenchymal disease processes (page 4669). Because the oligos were fluorescently labeled,

Whitesell et al. were also able to determine, or map, the location and distribution of the perfused oligos.

Davidson et al. teach a method for preparing viral vectors encoding small interfering RNA for use in gene silencing therapy of genes associated with neurodegenerative disorders, including spinocerebellar ataxia type 1 (SCA1) (see esp. paragraphs 180-185). The authors contemplate the use of their invention as a method for reducing the expression of a gene product (paragraph 5) such as that associated with SCA (see claims 23 and 48). Thus, Davidson teach the construction of siRNA expression cassettes (paragr. 136-156) and siRNA-encoding recombinant viruses (paragr 157-170) for general use *in vivo* via direct delivery to a mouse brain (paragr. 209).

It would have been obvious to one of ordinary skill in the art at the time the invention was made to develop siRNA encoding vectors, as taught by Xia et al. and Driscoll et al. for direct intracranial delivery into the brains of mice and other organisms to reduce the expression of dominant disease-causing genes such as mutant ataxin-1 to inhibit neurodegeneration associated with spinocerebellar ataxia type 1, as taught by Davidson et al. One of skill in the art would have been appraised of the correlation of ataxin-1 protein and SCA1 based on the teachings of Matilla et al., who teach that a mutant form of ataxin-1 is responsible for the physiological abnormalities associated with SCA1.

One would have been motivated to create such systems for delivering SCA1-targeting small interfering RNA into the brains of mice or rats because Matilla et al. teach that SCA1 has a genetic basis involving the expression of a mutant or toxic form of the SCA1 gene in Purkinje cells of the brain causing loss of these cells and an ataxic phenotype (page 5508).

One would have a reasonable expectation of success given that the combined teachings of Xia et al. Driscoll et al., and Whitesell et al. teach that systems for direct delivery of antisense RNA or vectors encoding siRNA (e.g. short hairpin RNA) can be used effectively to reduce gene expression in brain tissues and that the direct delivery with continuous infusion can result in potentially therapeutic levels and extensive brain uptake of antisense oligos (see Whitesell throughout), circumventing the obstacles observed with systemic administration through the blood stream. Furthermore, Davidson et al., encourage and teach the use of recombinant siRNA-encoding vectors to treat spinocerebellar ataxia type 1 (SCA1).

Thus in the absence of evidence to the contrary, the invention as a whole as claimed in the instant claims would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made.

Arguments considered:

Applicants argue (pp. 14–20) each of the applied references separately, asserting that each reference on its own fails to reasonably suggest or enable the claimed invention. Applicants also appear to suggest that the sheer number of applied references weigh against the obviousness of the claimed invention.

> MPEP §2145, Section IV states:
>
> One cannot show nonobviousness by attacking references individually where the rejections are based on combinations of references. *In re Keller*, 642 F.2d 413, 208 USPQ 871 (CCPA 1981); *In re Merck & Co., Inc.*, 800 F.2d 1091, 231 USPQ 375 (Fed. Cir. 1986).
>
> Reliance on a large number of references in a rejection does not, without more, weigh against the obviousness of the claimed invention. *In re Gorman*, 933 F.2d 982, 18 USPQ2d 1885 (Fed. Cir. 1991) (Court affirmed a rejection of a detailed claim to a candy sucker shaped like a thumb on a stick based on thirteen prior art references.).

Applicants also argue several limitations that are not claimed. Although the claims are interpreted in light of the specification, limitations from the specification are not read into the claims. See *In re Van Geuns*, 988 F.2d 1181, 26 USPQ2d 1057 (Fed. Cir. 1993).

Applicants argue that the applied references are unsuitable for the purpose of treating a neurodegenerative disease. However, these arguments fail to disqualify the references for what they taught or fairly suggested to one of skill in the art at the time the invention was made. It is not necessary that the applied references, taken alone or as a whole, suggest the combination to achieve Applicant's intended purpose of "treating." It is sufficient that the applied references taught one of skill in the art how to inhibit gene expression, particularly SCA1, in the brains of certain animals, or organisms, or "patients," and that the references do not suggest a combination that would be unsuitable for treating a neurodegenerative disorder in an organism. When considered together, the references provide sufficient motivation and ample information to use RNA interference as a tool to study the relationship between gene expression and neurodegenerative disease. Clearly, they provide examples of stereotactically implanted devices and direct brain injection for delivering siRNA into the brains of mice, a suitable animal model and "patient," as defined by the specification, to inhibit specific genes.

Accordingly, the instant rejection is maintained.

Prior Art not relied upon

The prior art made of record and not relied upon is considered pertinent to applicant's disclosure.

- Elsberry (WO 97/40874), who teaches a system for treating neurodegenerative disorders by brain infusion.
- Elsberry et al. (US Patent 5,735,814) and Elsberry et al. (US Patent 5,814,014), who teaches devices for treating neurodegenerative disorders by brain infusion. On page 27 of the instant application, Applicant states that these devices can be used to deliver small interfering RNA in accordance with the present invention.
- McSwiggen (US Patent Application Publication 2003/0190635), who teaches the preparation and use of small interfering RNA against beta secretase (BACE) to treat Alzheimer's disease.
- Powell et al. (US Patent 6,870,030), who teach antisense oligonucleotides for reducing the expression of aspartyl protease 2 (Asp2) for treatment of Alzheimer's disease.
- Dorri et al. (1997) *Exp. Neurology* 147:48-54, who teach a system for injecting antisense oligonucleotides combined with a fluorescent dye into the hippocampus of rats for alteration of neural activity.
- Zhang et al. (1996) *J. Mol. Neuroscience* 7:13-28, who teach a system for injecting FITC-labeled antisense oligonucleotides into the lateral cerebral ventricles of mice.

Response to Applicants' Arguments

Applicants' arguments presented on 1/5/06 not specifically addressed above are considered to be moot in view of Applicants' amendments to the claims and in view of the new and/or reiterated rejections stated herein, above.

Conclusion

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL.** See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Louis V. Wollenberger whose telephone number is 571-272-8144. The examiner can normally be reached on Mon–Fri, 8:00 am–4:30 pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's acting supervisor, Andrew Wang can be reached on 571-272-0811. The fax phone number for the organization where this application or proceeding is assigned is 703-872-9306.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval system (PAIR). Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR

system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

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Art Unit 1635
February 22, 2006

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1635